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(54) Title: TREATMENT OF CHRONIC FATIGUE SYNDROME AND FIBROMYALGIA SYNDROME

(57) Abstract: Chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) can be treated by the administration of Δ 5-androstan-3 β -ol-7,17 dione and metabolizable precursors thereof.

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TREATMENT OF CHRONIC FATIGUE SYNDROME AND FIBROMYALGIA SYNDROME

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This application claims the benefit of United States Provisional Application No. 60/250,227, filed November 30, 2000.

10

FIELD OF THE INVENTION

This invention broadly relates to the treatment of chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS). More specifically, the invention relates to prophylactic, modulatory, ameliorative and curative drug therapies for CFS and FMS.

15

BACKGROUND

Chronic fatigue syndrome (CFS) is a clinically defined condition characterized by severe disabling flu-like fatigue and a combination of symptoms that include impairment in concentration and short-term memory, sleep disturbances, and musculoskeletal pain.

20

Fibromyalgia syndrome (FMS) is a chronic rheumatic condition characterized by systemic body pain and uncontrollable fatigue. Many other symptoms are associated with FMS, such as headaches, sleep disorders and poor circulation.

25

CFS and FMS remain serious problems for a large segment of the general population. While many medications are commonly used to treat these conditions, there are no known medications which permanently resolve the symptoms of either CFS or FMS and many of the currently used medications produce undesirable side effects ranging from drowsiness and dizziness to addiction and liver damage.

Some of the more common medications employed to treat CFS and/or FMS include analgesics, hypnotics, immune suppressants and an array of herbal and dietary supplements.

5 Analgesics include nonsteroidal anti-inflammatory drugs. An analgesic that is sometimes prescribed for CFS and FMS patients is cyclobenzaprine. It is generally prescribed for the relief of skeletal muscle spasms.

Hypnotics used in the treatment of CFS and FMS include the benzodiazepines. Benzodiazepines are typically prescribed for CFS patients as a treatment for various sleep 10 disorders. Examples of benzodiazepines used in the treatment of CFS and FMS are Klonopin™, Valium™, Xanax™, Ativan™, and Dalmane™. A non-benzodiazepine hypnotic drug that has sometimes been prescribed to relieve sleep problems for CFS patients if Zolpidem™.

15 Immune suppressants prescribed to treat CFS and FMS include azathioprine. Such use is purely experimental and generally considered inappropriate for the treatment of CFS and FMS in view of the degree of toxicity associated with these agents.

20 Other drugs given to treat CFS and FMS include Naltrexone™, opioid antagonist, sodium retention agents, beta blockers, calcium channel blockers, histamine blockers, anti-depressants, allergy medications, and acute anxiety medications. Most of these drugs are either inappropriate for the treatment of CFS and FMS either because they are not effective or because of the significant side effects associated with their use.

25 A wide variety of herbal preparations, and dietary supplements have been suggested for use in alleviating the symptoms of CFS and/or FMS. One such herbal preparation is disclosed in United States Patent No. 5,919,460. Although the potential medicinal value of various herbs is promising, it is difficult, if not impossible, to assess the validity of scientific claims regarding these substances.

30 Other medications recently suggested for the treatment of CFS and/or FMS include buprenorphine (United States Patent No. 5,900,420) and various esters and salts of 4-hydroxybutyric acid (United States Patent No. 5,990,162).

United States Patent No. 5,935,949 discloses that the symptoms of CFS and FMS can be alleviated through androgen therapy. However, the prolonged administration of adrogens involves a number of undesirable side effects such as hirsutism in women.

5 While a number of options exist for the treatment of CFS and/or FMS, a need continues to exist for a composition that is effective in treating CFS and/or FMS in the absence of any significant undesirable side effects.

10 **SUMMARY OF THE INVENTION**

The invention is directed to the administration of $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof for the prophylactic, modulatory, ameliorative and curative treatment of chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS).

15

**DETAILED DESCRIPTION OF THE INVENTION
INCLUDING A BEST MODE**

20 Chronic fatigue syndrome and fibromyalgia syndrome can be treated by administering therapeutic amounts of the steroid $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof, such as $\Delta 5$ -androstene- 3β -acetyl-7,17 dione. Such treatment can be prophylactic, modulatory, ameliorative or curative in nature.

25 **The Compound**

30 The steroid $\Delta 5$ -androstene- 3β -ol-7,17 dione is a derivative of dehydroepiandrosterone (DHEA) which does not appreciably stimulate, increase or otherwise enhance the production of sex hormones. The steroid is commercially available from a number of sources including Steraloids, Inc. of Wilton, New Hampshire. A number of procedures are available for synthesizing $\Delta 5$ -androstene- 3β -ol-7,17 dione from DHEA, with one such procedure described in United States Patent No. 5,296,481.

Precursors of $\Delta 5$ -androstene- 3β -ol-7,17 dione may also be usefully employed in the treatment of hypothyroidism. Such precursors are readily metabolized *in vivo* to the active $\Delta 5$ -androstene- 3β -ol-7,17 dione. One example of such a metabolizable precursor is the commercially available $\Delta 5$ -androstene- 3β -acetyl-7,17 dione. The 3β -acetyl group is

5 hydrolyzed *in vivo* by esterases located in the blood and various tissue to produce the active $\Delta 5$ -androstene- 3β -ol-7,17 dione, and is believed to be less susceptible to oxidation during the manufacturing process than the hydroxy group found on the active $\Delta 5$ -androstene- 3β -ol-7,17 dione. Other metabolizable precursors include $\Delta 5$ -androstene- 3β , 17 β -diol-7-one, $\Delta 5$ -androstene- 3β , 7 α -diol-17-one, $\Delta 5$ -androstene- 3β , 7 β -diol-17-one and the corresponding

10 acetyl esters of these steroids.

Administration

Administration Route

15

The $\Delta 5$ Androstene-3-acetyl-7,17-dione can be administered by virtually any of the commonly accepted practices for the administration of pharmaceutical preparations including specifically, but not exclusively, mucosal administration, oral consumption, ocular administration, subcutaneous injection, transdermal administration, etc. Oral administration

20 is generally preferred.

Mucosal administration of the steroid includes such routes as buccal, endotracheal, nasal, pharyngeal, rectal, sublingual, vaginal, etc. For administration through the buccal/sublingual/pharyngeal/endotracheal mucosal, the steroid may be formulated as an emulsion, gum, lozenge, spray, tablet or an inclusion complex such as cyclodextrin inclusion complexes. Nasal administration is conveniently conducted through the use of a sniffing powder or nasal spray. For rectal and vaginal administration the steroid may be formulated as a cream, douche, enema or suppository.

25

30 Oral consumption of the steroid may be effected by incorporating the steroid into a food or drink, or formulating the steroid into a chewable or swallowable tablet or capsule.

Ocular administration may be effected by incorporating the steroid into a solution or suspension adapted for ocular application such as drops or sprays.

Subcutaneous administration involves incorporating the steroid into a
5 pharmaceutically acceptable and injectable carrier.

For transdermal administration, the steroid may be conveniently incorporated into a lipophilic carrier and formulated as a topical creme or adhesive patch.

10 **Dose Rate**

The range of dosages and dose rates effective for achieving the desired biological response may be determined in accordance with standard industry practices. These ranges can be expected to differ depending upon numerous well known factors such as the severity
15 and/or chronicity of the disease, the species of the patient, the histopathologic type of the patient, the weight of the patient, the length and course of the treatment, the responsiveness of the patient, and whether the desired response is prophylactic, modulatory, ameliorative or curative in nature.

20 The treatment of CFS and FMS is often idiosyncratic and adjustment of dosages and dose rate is well within the level of one having skill in the art.

Subject

25 The subject can be a human or a pet such as a cat, dog or horse. The treatment is also suitable for use with commercially valuable livestock such as cattle, pigs and sheep; as well as exotic mammals such as those found in zoos and circuses.

EXPERIMENTAL***Experiment 1***

5 One male subject, aged 73, recently diagnosed with chronic fatigue syndrome by CDC criteria, orally consumed 100 mg capsules of $\Delta 5$ -androstene-3-acetyl-7,17-dione twice daily for two months. Upon a visit to his personal physician, he reported an 80% improvement in his symptoms of fatigue and felt more mentally alert. As testament to his improvement, he reported to his physician that he had just finished building a 20' x 30'
10 addition to his barn, something, he said, he would not have and could not have done prior to taking $\Delta 5$ -androstene-3-acetyl-7,17-dione.

I claim:

1. A method of treating chronic fatigue syndrome and fibromyalgia syndrome comprising administering a therapeutically effective amount of a compound to a mammal in need of such treatment wherein the compound is selected from $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof.
2. The method of claim 1 wherein the subject is a mammal.
3. The method of claim 2 wherein the subject is a dog or a cat.
4. The method of claim 2 wherein the subject is a human.
5. The method of claim 1 wherein the compound is administered orally.
6. The method of claim 1 wherein the compound is $\Delta 5$ -androstene- 3β -acetyl-7,17 dione.
7. The method of claim 1 wherein the compound is administered daily.
8. A method of treating chronic fatigue syndrome comprising administering a therapeutically effective amount of a compound to a mammal in need of such treatment wherein the compound is selected from $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof.
9. A method of treating fibromyalgia syndrome comprising administering a therapeutically effective amount of a compound to a mammal in need of such treatment wherein the compound is selected from $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof.
10. A method of prophylactically protecting against the onset of chronic fatigue syndrome or fibromyalgia syndrome comprising administering a prophylactically effective amount of a compound to a mammal desiring prophylactic protection against the onset of

chronic fatigue syndrome or fibromyalgia syndrome wherein the compound is selected from $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof.

11. The method of claim 10 wherein the subject is a mammal.
12. The method of claim 11 wherein the subject is a dog or a cat.
13. The method of claim 11 wherein the subject is a human.
14. The method of claim 10 wherein the compound is administered orally.
15. The method of claim 10 wherein the compound is $\Delta 5$ -androstene- 3β -acetyl-7,17 dione.
16. The method of claim 10 wherein the compound is administered daily.
17. A method of prophylactically protecting against the onset of chronic fatigue syndrome comprising administering a prophylactically effective amount of a compound to a mammal desiring prophylactic protection against the onset of chronic fatigue syndrome or fibromyalgia syndrome wherein the compound is selected from $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof.
18. A method of prophylactically protecting against the onset of fibromyalgia syndrome comprising administering a prophylactically effective amount of a compound to a mammal desiring prophylactic protection against the onset of chronic fatigue syndrome or fibromyalgia syndrome wherein the compound is selected from $\Delta 5$ -androstene- 3β -ol-7,17 dione and metabolizable precursors thereof.

INTERNATIONAL SEARCH REPORT

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PCT/US01/46241

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/56

US CL : 514/178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/178

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,296,481 A (PARTRIDGE et al.) 22 March 1994 (22.03.94), see the entire document.	1-18
A	US 5,935,949 A (WHITE) 10 August 1999 (10.08.99), see the entire document.	1-18

Further documents are listed in the continuation of Box C.

See patent family annex.

"A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"A"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

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